eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Preventive Effects of Phenolic Compound Extra Virgin Olive Oil (EVOO) on the Incidence of Hand Foot Syndrome Induced Capecitabine

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ARTICLE INFO

Keywords:
Hand foot syndrome
Capecitabine
Extra virgin olive oil
Phenolic compound
Antioxidant

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/bsm.v6i1.432

ABSTRACT

Hand foot syndrome (HFS) is a reaction that occurs on the skin of the palms and soles. feet, caused by the toxicity of chemotherapy drugs with symptoms such as tingling, pain, erythema, dry skin, swelling, increased pigmentation and itching. This condition is still a problem in the treatment of patients given capecitabine. Although HFS does not cause death, in severe cases it can affect the quality of treatment and interfere with daily activities. The cause of HFS is still unclear but from research it is known that capecitabine and its metabolites will increase the expression of the COX-2 enzyme, inhibit the arachidonic pathway, increase PGE2 activity, causing inflammatory reactions in the form of erythema, edema and pain. The phenolic components contained in EVOO, namely oleocanthal and hydroxytyrosol compounds in several studies have the same properties as celecoxib and ibuprofen as anti-COX-2, will inhibit the arachidonic synthesis pathway, reduce prostaglandin activity and reduce inflammatory reactions.

1. Introduction

Hand Foot Syndrome (HFS) is a skin reaction that occurs on the palms of the hands and feet, caused by the toxicity of chemotherapy drugs with symptoms such as tingling, pain, erythema, dry skin, swelling, increased pigmentation and itching.[1,2] The incidence of HFS varies from 6-60% with severe cases 10-20%.[3] Chemotherapy drugs that most often cause HFS are capecitabine which is widely used in patients with breast cancer and colorectal cancer with incidence rates varying between 50-60% with severe cases 10-70% [1,2,3,4,5,6]. Hand foot syndrome is reversible and not life-threatening, but it often affects the quality of treatment and the patient's life.[1] The mechanism of HFS is still unclear, one of the hypotheses of HFS is the overexpression of COX-2 which will increase PGE2 activity and result in an inflammatory reaction in the form of erythema, pain and edema. The theory of the occurrence of HFS due to an inflammatory process has been proven by the presence of signs of inflammation in tissues that have HFS in the form of dilatation of blood vessels, edema, and infiltration of white blood cells (leukocytes).[3] Several studies have been carried out to prevent the occurrence of HFS by giving oral anti-COX-2 namely celecoxib along with capecitabine as

done by Zang et al and Lin et al. From this study, it was found that the incidence of HFS degree 1 was reduced by 43% and HFS degree 2 was 28% [4,5]. Extra virgin olive oil (EVOO) is a type of olive oil that is often included in the daily diet of the Mediterranean population, consuming an average of 25-30 mL per day, generally in salad dressings and cooked foods [7]. Contains a major component of monounsaturated fatty acids (MUFA) 98-99% and minor components of phenolics, phytosterols, tocopherols, and squalene in small amounts 1-2% [8]. Although the amount of this component is small, it has high biological activity [9,10].

Capecitabine & its metabolites

Capecitabine and its breakdown products directly or indirectly activate the COX-2 inflammatory pathway leading to white blood cell infiltration, dilation of blood vessels, and edema in HFS-affected tissues. Cyclooxygenase has 2 forms, namely COX-1 and COX-2 where COX-1 is widely found in normal tissues and is often referred to as a house guard gene while COX-2 has an important role in the synthesis of prostaglandins (prostaglandins, prostacyclins, thromboxane, and eicosanoids) that are associated with pain and inflammation reaction.[11] COX-1 has 576 amino acids, while COX-2 has 581 amino acids. COX-1 has three oligosaccharides, one oligosaccharide plays a role in protein folding while COX-2 has four oligosaccharides, where one oligosaccharide plays a role in protein folding and the fourth oligosaccharide plays a role in protein degradation. COX-2 is an enzyme released at the site of the wound that produces a hormone-like substance called prostaglandin E2 (PGE2) that stimulates pain and inflammation. PGE2 causes arterial dilatation and increases microvascular permeability, causing edema and erythema. PGE2 also stimulates peripheral sensory neurons that cause pain.[3,12] The effect of doses of chemotherapeutic agents that are given repeatedly or given high doses results in more cumulative damage to keratinocytes because they have a fast turnover time. Cytotoxic drugs are also excreted through sweat, making the palms and soles more susceptible to HFS due to the abundance of sweat glands in both extremities. There is also an assumption that areas subject to friction or trauma may have higher concentrations of chemotherapeutic agents as a result of the thickening of the papillary dermis which is rich in capillaries.[13] Inflammatory reaction through the COX 2 began their involvement phospholipid membrane as a result of trauma or infection process which will enable arachidonate acid by the enzyme phospholipase A2. The arachidonic acid formed will activate prostaglandins in the presence of the COX-2 enzyme. Prostaglandins that are formed will cause dilation and edema, also accompanied by pain.[14]

Olive oil (Olive)

Olive oil is an oil extracted from olives (*Olea europea*). The countries that produce the most olives are the Mediterranean countries, Spain, Italy, and the United States. Most of this Olive oil is a food ingredient or traditional diet that is used daily. The composition of olive oil is influenced by the shape of the fruit, the origin of the production area and how it is processed.[15] Features of olive oil which have good quality have a fragrant and subtle smell. Many studies on olive oil which are beneficial for health have been carried out both epidemiologically and clinically.[16-25] Studies describe long-term administration of a diet containing EVOO reduces the incidence of stroke in a Spanish population prone to cardiovascular disease and reduces the risk of type 2 diabetes in obese patients [26] the PREDIMED-Malaga trial showed that MD supplemented with EVOO slowed the natural progression of non-alcoholic fatty liver disease (NAFLD).[27-30] A three-city study showed that the incidence of stroke was reduced in patients fed a Mediterranean diet compared to patients not given olive oil. [31-35]

Composition of olive oil

The chemical composition of olive oil varies depending on extract technology and is influenced by the shape of the olive. Each filtering process will reduce the number of components contained therein. Olive oil that has undergone filtering, its components will be reduced and does not contain vitamins, polyphenols, phytosterols, while oil that is only squeezed without filtering contains many components of vitamins that are important for health. *Virgin extra olive oil* (VOO) is

olive oil that has been squeezed twice while EVOO has only been squeezed once, so it has more minor components than VOO and is widely used in a healthy diet.

Olive oil can be classified into two fractions from a quantitative point of view. The main fraction 98 -99% consists mainly of saponifiable triacylglycerols. This major component 60-84% consists of oleic acid (MUFA) and linoleic acid which are the main essential fatty acids and polyunsaturated acids (PUFA) which are abundant in our food, namely 3-21%. Other major components are palmitic acid, stearic acid and -linolenic acid.[36-38] Minor components are found 1-2% of all components of olive oil, consisting of components that cannot be sanitized/absorbed, namely hydrocarbons, sterols, terpenic alcohols, tocopherols and components that can be sanitized, namely phenolic components consisting of 4 groups, namely flavonoids, lignans, secoiridoids, and simple phenolics. Flavanoids were only found in very low levels, and lignans were found in more significant levels, while the main phenolics were simple phenolics consisting of tyrosol, hydroxytyrosol and secoiridoids, which are compounds derived from oleuropein glucosides and ligstrosides. These phenolic components, although small in number, provide important biological activity.[39]

Table 1. Composition of components of *Minor Virgin Olive Oil* (VOO)

Minor component composition of VOO		
Subfraction	Component	Concentration (mg/kg)
Unsaponifiable		
Hydrocarbons	Squalene β-Carotene Polycyclic aromatic Hydrocarbons	200-7500 0.3-0.7 Traces
Sterols	β-Sitosterol Campesterol Δ7-Stigmasterol Brassicasterol	1800-2600 <4.0% of total sterols <0.5% of total sterols <0.1% of total sterols
Terpenic dialcohols	Erythrodiol + uvaol	6-10+8
Tocopherols	α-Tocopherol β+γ-Tocopherol Δ- Tocopherol	60-200 3% of total tocopherols <2% of total tocopherols
Phenolic compounds	Tyrosol Hydroxytyrosol Caffeic acid Oleuropein	50-800 (total phenols)
Others	Flavor components	Traces

Phenolic components

It is the main component of minor components of olive oil, consisting of tyrosol, hydroxytyrosol, oleocanthal, oleuropein. Polyphenols are found in many plants such as fruits, seeds, nuts, herbs and leaves with different levels and biological activities. Many nutritional and vitamin products are manufactured containing polyphenols, due to their antioxidant and anti-inflammatory effects. The phenolic content of olive oil varies widely. Generally, EVOO contains the highest levels of phenolic compounds, but this also varies depending on the conditions under which the olives are grown and harvested (e.g. soil conditions, fruit ripeness) and storage conditions, as well as depending on the manufacturing technology, levels are substantially reduced by chemical processes. For example, more phenolic components are found in *extra virgin olive oil* (EVOO) than in *refined virgin olive oil* (RVOO).

The total phenolic component in olive oil varies between 800 mg/kg and 1 g/kg. In the EVOO preparation, the phenol level of 232 ± 15 mg/kg was higher than that of the ROO, which was 62 ± 12 mg/kg. *Polyphenols* taken daily ranged from 0.1 to 1.0 grams from foods or drinks containing olive oil. EFSA (European Food Safety Authority) in November 2011

stated that the benefits of using olive oil because it is rich in components *phenolic* and recommends using 5 mg of *hydroxytyrosol* and its derivatives contained in olive oil every day. It is known that the phenolic content is reduced by the heating process.[40] In young olives, the composition of phenolic components is higher than after the fruit is ripe. The phenolic content in the form of oleuropein which contains hydroxytyrosol and oleanolic acid as much as 14%, while after the fruit is ripe, the oleuropein content decreases and the hydroxytyrosol level increases. After being processed into olive oil, the concentration of hydroxytyrosol in olive oil is 1.4 -5.6 mg/L, in *extra virgin olive oil* 14.42 mg/kg and 1.74 mg/kg in *refined virgin oil.* While the tyrosol content in olive oil is 4.69 mg/kg, in *extra virgin olive oil* 27.45 mg/kg and *refined virgin olive oil* 2.98 mg/kg. The level of oleuropein in olive oil is 2.3 mg/kg and in *extra virgin olive oil* 2.04 mg/kg. Because these phenolic components are easily absorbed, it is difficult to calculate the actual levels.

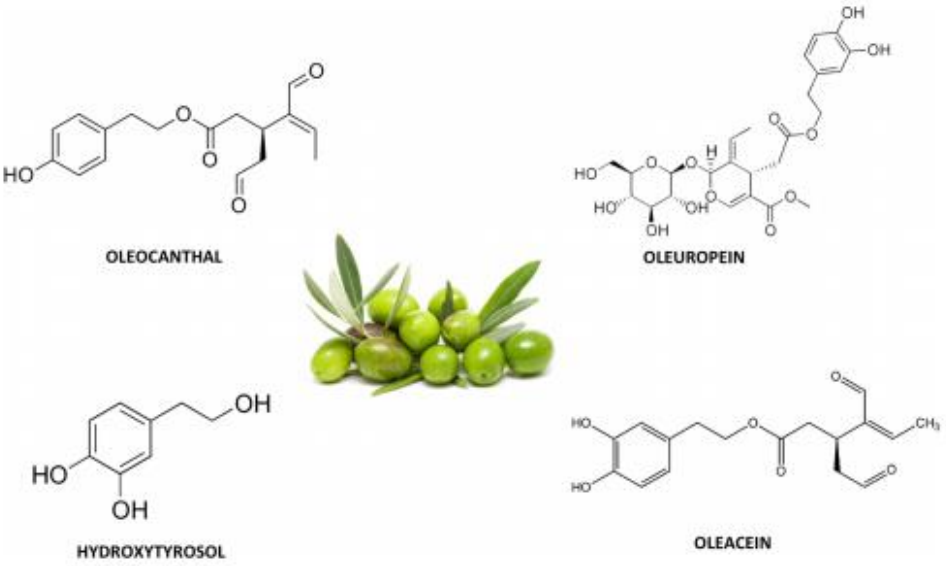

Figure 1. Structure of the main phenolic components

In addition to the composition and concentration in EVOO, the effectiveness of phenolic components is also influenced by several important things, namely absorption, metabolic processes, distribution and elimination to achieve good effectiveness in tissues and organs (sincerely Lucas). The EVOO storage process is also an important consideration to maintain the stability of the quality of its health effects. A good storage period of 12-18 months, at low temperatures, reduced oxygen and light exposure [37]

Oleocanthal

Decarboxy methyl ligstroside aglycone or so-called Oleocanthal was first documented in the literature as a phenolic compound contained in VOO in the early 90s, and 2003 reported that oleocanthal is a phenolic responsible for the pungent taste and pungent throat. The oleocanthal content in EVOO varies from 0.2 to 498 mg/kg[35]. This variation is influenced by several factors, namely extraction method, geographical area of olive growth, olive tree cultivar, olive cultivation technique, olive fruit maturity, olive oil manufacturing process, storage process.[35] The higher the oleocanthal content, the hotter the VOO taste.

Many researchers do explore these compounds against sifat2 pharmacological and clinical manual as an anti-inflammatory, anti-cancer, rheumatic diseases and complications neurogeneatif.[33] In vitro clearly shows that oleocanthal and hydroxytyrosol are natural NSAIDs that inhibit the enzyme COX-1 and COX 2, the same as the mother nature propene as NSAIDs synthesis with a dose-dependent manner38. The COX2 enzyme inhibitory activity of oleocanthal was 41-57% stronger than that of ibuprofen, which was 13-18%.

With the power weakens from oleocanthal to the activity of COX 2 resulted in disruption of acid metabolism arachidonate, Prostaglandins and thromboxane so that the inflammatory process is disrupted and can reduce chronic inflammation so that the data of cases of cancer of the breast, prostate, lung and gastrointestinal in populations of the Mediterranean is lower than the western population [21-25] and also inhibits cell proliferation, migration and invasion [26-28]. It is known that in both human and animal studies, one COX 2 enzyme is involved in the pathogenesis of several cancers because oleocanthal is a naturallyCOX inhibitor occurring [29-33]. Because the effect of oleocanthal inhibits the synthesis or activity of prostaglandins, anything related to increased prostaglandin activity can be inhibited or overcome by administering oleocanthal which is found in EVOO at high enough levels. Oleocanthal has a neuroprotective effect against degenerative diseases such as Alzheimer's disease and Parkinson's disease. This disease can interfere with memory, cognition, motor coordination, sociality, gait and daily activities. The study found that oleocanthal reduces astrocyte activity and levels of IL-1β in the brain of animal models of Alzheimer's disease[23] oleocanthal also known to interfere with the aggregation pathway and thus protect neurodegeneration clearance of amyloid peptides. In OA and RA, oleocanthal can inhibit local inflammation in cartilage and prevent the inflammatory cascade associated with degenerative inflammatory joint disease[24]

Hydroxytyrosol

Hydroxytyrosol (HT) compounds are also a major phenolic component that is widely used for chronic diseases. This compound is derived from the hydrolysis of oleuropein which occurs naturally during the ripening process of olives and as a result of prolonged storage of the oil. The content in EVOO 100-300 ppm obtained in the natural olive oil manufacturing process[9]. Hydroxy tyrosol has an antioxidant effect, a powerful anti-inflammatory, anti-thrombotic, anti-cancer anti-microbial passage [22]. Many studies on the effectiveness of HT have been carried out in animals and only a few in humans regarding the adsorption, distribution, metabolism and excretion.[25-27]

In the study was hydroxytyrosol with levels of 12.5 to 25 µ M decreased the expression of iNOS, COX2, endoperoxides prostaglandin synthase-2 (PTGS2), chemokines (CCL5 / RANTES, CXC10 / IP10dan CCl4 / MIP1β),IL 1α and matrix metapeptidase- 9(MMP-9) gene in the macrophage cell line RAW264.7, due to the stimulating effect of the pro-inflammatory molecule LPS (lipopolysaccharide) [40]. When HT was given at a dose of 50 M will inhibit Nuclear factor -κB (NF-κB). Data reported on the use of HT at a dose of 100 µM can inhibit the production of $O2^-$ (superoxide anions) and decrease the expression of COX2 and PGE2 release [31]. Hydroxytyrosol has been reported to have significant anti-inflammatory properties in animal models of inflammation and attenuate the expression of TNF -α and IL-1β which are pro-inflammatory cytokines.[32] In vitro has been reported that weaken hydroxytyrosol iNOS, COX2, TNF-α for LPS stimulation in THP-1 monocytes humans [33]. Maiuri reported hydroxytyrosol down-regulated gene expression of iNOS and COX 2 to prevent the activation of NF-κB, STAT-1α and IRF-1 mediated by LPS-induced ROS generation [34] while Rossilo et al reported hydroxytyrosol and hydroxytyrosol acetate has anti-inflammatory effects of IL-β in by stimulating human SW982 cells were characterized by decreasing inflammatory mediators such as MMP-1, MMP-3, COX-2, mPGES-1, IL-6 and TNF-α [38]. It was also reported by Scoditti et al that HT incorporated into nutrition in certain concentrations can reduce the induction of MMP-9 and COX-2 in activated human monocytes through inhibition of PKCA and PKCB1, thereby exhibiting anti-inflammatory properties of HT and explaining the vascular protective effect of HT. phenolic components of the Mediterranean diet [39]. In the elderly who have been using long-term low-dose aspirin therapy with synthetic anti-inflammatory drugs such as COX-2 as celecoxib, there is a risk of damage to the stomach due to its irritating effect. By giving HT to elderly people who use low-dose aspirin, it turns out that besides being able to reduce anti-inflammatory, it can also prevent damage to the stomach. HT as a natural anti-inflammatory can be given in combination with synthetic anti-inflammatory drugs, both short-acting

and long-acting in the long term, providing effective and safe results.[40]

2. Conclusion

Oleocanthal and Hydroxytyrosol compounds are phenolic components present in EVOO which have high anti-inflammatory properties with high anti-inflammatory properties. inhibiting the COX-2 pathway, interfering with the synthesis of the arachidonic enzyme, inhibiting the PGE2 enzyme, and ultimately inhibiting the inflammatory process and preventing the occurrence of hand foot syndrome.

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